Ultrasound-guided High Intensity Focused Ultrasound to treat Twin-Twin Transfusion Syndrome (USgHIFU-TTTS study)

Participant Information Sheet

You are being invited to take part in a research study. Before you decide whether or not to take part, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Talk to others about the study if you wish. Contact us is there is anything that is not clear to you or if you would like more information. Take time to decide whether you want to take part in the study or not.

What is the purpose of the study?

Some identical twins share a placenta. These are called monochorionic ("one placenta") twins. Within this shared placenta, in 95% cases, there are connections between the twins' blood vessels. These connections can be between two arteries, two veins, or an artery and a vein. Connections between an artery and a vein can allow one twin to receive too much blood and the other too little, a condition called **t**win-**t**win **t**ransfusion **s**yndrome (TTTS). This study is looking at whether it is possible to use a non-invasive treatment, **u**ltra**s**ound **g**uided **h**igh **i**ntensity **f**ocused **u**ltrasound (USgHIFU), to block these connections between the arteries and veins in the placenta. USgHIFU has not been used to do this before this study, and our research group is using a custom-made USgHIFU system to see if this new technique could be both safe and effective. This would show that USgHIFU could be a treatment for TTTS.

Why could using USgHIFU to treat TTTS be important?

If TTTS develops, women may be offered treatment. This would either be fetoscopic laser, where a fine laser is put into the womb to block the connections between the twins' circulations, or selective termination, where a small instrument is put into the womb to block the flow in the umbilical cord of one twin. Fetoscopic laser is the only treatment which aims to keep both twins alive until delivery. Both treatments are invasive, and so carry risks of miscarriage, early rupture of membranes or infection developing within the womb. Fetoscopic laser is not usually offered until after 18^{+0} weeks' gestation, but in some cases can be performed as early as 16^{+0}. When TTTS is diagnosed before 18^{+0} weeks' gestation, sometimes parents and doctors choose a watch and wait strategy until the pregnancy is more developed, during which time the twins can die from the TTTS.

However, it may be possible to use non-invasive USgHIFU to do the same thing as fetoscopic laser, but without the risks of surgery. Ultrasound imaging is used to guide the HIFU treatment by finding blood vessels in the placenta which need to be blocked. HIFU works by focusing a beam of ultrasound energy to "burn" a small volume of tissue at a specific site in the body – a bit like using a magnifying

glass to focus sunlight and burn a small hole in a piece of paper. HIFU has been used to treat other medical conditions for many years. Just like laser, USgHIFU would aim to keep both twins alive until delivery. HIFU could be offered as a treatment for TTTS at earlier gestational ages than fetoscopic laser, avoiding the need for a watch and wait strategy.

Why have I been invited to take part?

You have been invited to take part because you are pregnant with monochorionic diamniotic (MCDA) twins. This means your twins have one placenta but two amniotic sacs. You are between 12^{+0} and 17^{+6} weeks' gestation, and there is evidence of TTTS affecting your pregnancy. USgHIFU may, therefore, be a suitable treatment for you and your twins.

Do I have to take part?

No, it is up to you to decide whether to take part. If you do decide to take part, you will be given this information sheet to keep and asked to sign a consent form. If you decide to take part, you are still free to withdraw your consent at any time without giving a reason. Deciding to not take part will not affect your medical care or legal rights in any way.

What will happen if I decide to take part?

If you think you would like to take part, the next step is to check that this study is right for you – in other words, check your eligibility. We will ask you questions about yourself, your general health and details about this/past pregnancies. We also need to make sure we can find the connections between arteries and veins in your placenta using ultrasound imaging, otherwise we will not be able to target the HIFU where it needs to go (this is not something that is normally done as part of your NHS care). To find this out, we will ask you to first take part in a related, but separate, study – the "Twin Placental Mapping Study". In this study, we would perform an ultrasound scan at Queen Charlotte's and Chelsea Hospital, which would look at the blood vessels in your placenta. The research team who gave you this leaflet will have given you a separate leaflet about that study, and will take consent from you to enter that study if you agree.

After this, we will explain the findings of the twin placental mapping study to you and tell you whether we can offer you HIFU treatment. We will explain the HIFU treatment to you in greater detail. You will have the opportunity to ask any questions you have regarding the study. We will also discuss all the other treatment options that you have as part of NHS care. Queen Charlotte's and Chelsea Hospital is a tertiary referral centre for fetal medicine which sees many women with twins and TTTS every year, and if you choose one of the treatment options available to you through the NHS then we are able to carry that out for you. If you decide that you would like to go ahead with the HIFU treatment, we will discuss the timing of the treatment with you, so you will have enough time to consider your decision. The treatment window for TTTS can be very small so we may offer to treat you with HIFU on the same/next day, or we may be able to delay the treatment for a few days.

After this discussion, unless you are having same day treatment, you will leave the department with an appointment to come back for HIFU treatment. If you are having next day treatment, we can provide nearby accommodation for you and the person who comes with you, if you would prefer that to travelling home and back again. We will pay the travel expenses for you and another person you would like to bring with you for support each time you come for a research study visit.

Before the appointment to have the HIFU treatment, we will go through a consent form with you to gain your permission to enter you into the research study and to treat you with HIFU.

We will inform your GP about your participation in the study.

What happens during the HIFU treatment?

Before we do any HIFU treatment, we will repeat the ultrasound scan of your twins and placenta, and if treatment is still needed, and you still wish to have HIFU treatment, we will ask for your written consent to enrol you in the study. Once you have given us your consent, we will proceed with the HIFU treatment. You will then be asked to lie on a medical couch, similar to the ones you lie on during an ultrasound scan. ***Treatment is typically 2 hours, but in some cases may take up to 4-6 hours.*** In exceptional cases we may take a break overnight and finish treating the next day. ***We can stop and start as often as you need to for your comfort***.

The research team, which includes fetal medicine specialists, will use ultrasound imaging to find the exact position of the blood vessels in the placenta that they need to block (usually about 5-10). The USgHIFU device will be precisely positioned by a small robotic arm. You shouldn't feel the HIFU energy passing through your body. Treatments will be delivered as a series of short bursts of heating (typically 5 seconds long). Up to 6 bursts will be placed next to each other, typically with 5 second gaps between each, so ***the treatment of one blood vessel should last 20 – 60 seconds***. ***During HIFU treatments, you will have a handheld device to stop the treatment immediately for any reason you want to.*** There will be pauses between each treatment series while we check the results, make sure you and your babies are well and plan the exposure of the next target to block. ***Because we need to plan treatments carefully, these pauses may typically be 10-20 minutes, but because this is a new treatment, they could be up to an hour***. If you are in pain, we can give you painkiller tablets.

What happens after the HIFU treatment cycle is finished?

We will admit you overnight for observation and provide nearby accommodation for the person who has come with you. During this time, we will check that you are not in pain and monitor for complications of the treatment or TTTS to you or your babies. The following day we will perform another ultrasound to check on your twins and look at the placenta again. You will be invited to talk (this will be recorded) to one of our research team about the experience of being diagnosed with TTTS and treated with HIFU (a research interview). If all is well after this, you will go home. We anticipate that the time required to complete a USgHIFU treatment cycle should be one to two hours, but in exceptional circumstances HIFU exposure series could be spaced over a period of 72 hours.

We will ***ask you to come back to Queen Charlotte's and Chelsea hospital 3, 7 and 14 days after the HIFU treatment*** cycle has been completed for additional ultrasound examinations to check on your and your twins' progress. If the medical team decide the first treatment cycle needs to be repeated, you will be asked to give your consent for further treatments cycles as required. We will pay for your travel on each occasion. After that, you can return to the normal pattern of antenatal care and ultrasound examinations at your local hospital or referral centre.

After your due date, the research team will contact the hospital(s) where you were looked after during your pregnancy to record details of you and your babies' health during pregnancy and delivery. If you deliver at Queen Charlotte's and Chelsea or St Mary's hospital, we may take a photograph of the surface of your placenta after delivery. You will also be contacted after your due date to take part in a second research interview about your experience of participation in the research study.

<u>If you wish to stop taking part in the study completely, you may need to be seen one last time for an assessment.</u>

Research interviews (optional)

As part of this study, we would like to interview you on two occasions to see what your thoughts are about being part of a research study and to address questions relating to overall treatment acceptability, and how you think the study was carried out. Additionally, we would like to find out what your experience was of being diagnosed with and treated for TTTS and participating in research study during pregnancy. The first research interviews will be carried out during the Second Study Assessment, and the second research interview will be carried out 4 to 6 months after you've given birth – at a time convenient to yourself. These interviews will be conducted by an experienced research interviewer based at the Centre for Trials Research, Cardiff University.

During the research interviews, the conversations will be recorded on an encrypted device and the audio files transferred to secure Cardiff University computers. The audio recording will then be deleted from the device. The interview will be transcribed by a member of the Centre for Trials Research, Cardiff University. Only people working on the study will have access to the recording and transcripts. Once the recording has been transcribed and checked, the recording will be deleted from the computers. At the end of the study, all transcripts will be passed back to Imperial College London for archiving for 25 years..

We would expect to publish direct quotations from these interviews. At no point will real names be included, and we will preserve the anonymity of participants when publishing data from interviews. This may include the use of pseudonyms or changing identifiable features of the data to prevent identification.

Diaries

We will ask you to complete a symptom and appointment diary for the 14 days following the first USgHIFU treatment cycle.

We will also ask you to maintain a diary during the time between the two research interviews (from the end of the USgHIFU treatment cycle until 4 to 6 months after birth). In this diary you would be able to record key thoughts, events, and/or experiences that you would like to communicate to the research). This diary can be in the form of audio/video recordings if you wish.

Will I be paid to take part?

No, you will not be paid to take part in this study, but we will reimburse travel costs and provide accommodation where required. Please note that if you wish to claim reimbursement for travel costs incurred by taking part in the study, your personal details (home address and bank details) will be shared with Imperial College London's finance department. Your information will be securely stored within the finance department according to the University's financial procedures.

If I take part will I be able to have other treatment for TTTS?

Yes. If you do decide to take part, you will still be able to have treatment with fetoscopic laser, or opt for selective termination, at a later time if these options become suitable for you. If needed, we could perform these additional treatments at Queen Charlotte's and Chelsea Hospital.

What are the possible benefits of taking part?

Being part of this study may allow you to have a treatment for TTTS where no other treatment could be offered because of the early gestational age at which the TTTS was diagnosed. This study may also allow you to have a treatment for TTTS which is non-invasive, avoiding the risks of miscarriage, infection and preterm rupture of membranes associated with fetoscopic laser or selective termination. This treatment aims to keep both babies alive until delivery, but because this is research we don't yet know how well it will work

What are the possible disadvantages of taking part?

Ultrasound scans are not believed to have any side effects and are a routine part of the care of pregnant women. Women pregnant with twins usually have quite frequent ultrasound scans in pregnancy.

You will need to lie flat and still for the ultrasound scans and USgHIFU treatments, so if you are unable to do this without discomfort, you may find this difficult.

You will need to travel back and forth between your home and Queen Charlotte's and Chelsea Hospital in London on at least 4 occasions and be away from home around the time of the HIFU treatment. We will reimburse you financially for your travel and provide accommodation, but this may be inconvenient to you.

Although we have studied this technique in laboratory models and believe the treatment will work very well based on this work, we do not know if it is going to be possible to block blood vessels in the

human placenta, so you may not experience any clinical benefit. As a result, you may then need to have invasive treatments to treat the TTTS.

Potential minor complications resulting from the HIFU treatment are: pain and/or reddening of the skin at the treated area during treatment, or pain due to lying in one position for an extended period. We will offer you any medication or other treatment needed to control these symptoms if they occur.

Potential major complications from the HIFU treatment are second or third degree abdominal skin burns, nerve damage (e.g. sciatica), injury to internal organs (the bladder and the bowel), bleeding from the placenta and burns to one or both of the twins. We will try to avoid all these complications by careful planning and monitoring of your treatment. If we suspect any of these complications have occurred, we will admit you to hospital and carry out the appropriate tests to find out what has happened. We will offer you any treatment needed for the complications.

Who is the research team?

The research team is led by Dr Christoph Lees, Head of Fetal Medicine at Centre for Fetal Care, Queen Charlotte's and Chelsea Hospital. Professor Philip Bennett, Director of the Institute of Reproductive and Developmental Biology, Imperial College London is also part of the team. Both are fetal medicine experts with extensive research experience. Professor Gail ter Haar and Dr Ian Rivens, of the Institute of Cancer Research, are experts in medical physics, and have extensive research experience in developing new uses for HIFU. The study is being managed by the Centre for Trials Research, Cardiff University.

What will happen to the results of the study?

At the end of the research we will be able to inform you of the study results, if you wish. You will be given the option to provide an email address if you wish to be informed of the results of the study. A summary sheet of results will be emailed to you (by the research team based at Imperial College London) once the results have been finalised. We will not contact you for more than 5 years after the study, for this or any other reason related to this study or participation in other related research. The results may be presented at medical conferences or published in medical journals. You will not be identified in any presentation or publication, although anonymised ultrasound images of your placenta may be shown. All information related to clinical studies in pregnancy is kept in secure storage for at least 25 years (see below).

Will my participation in the study be kept confidential?

Yes. All the information we collect during the research will be kept confidential and there are strict laws which safeguard your privacy at every stage (see below). Pseudo-anonymised data (this means only labelled with a study code, not your name or any other personally-identifiable data) related to the HIFU treatments and any positive or negative outcomes observed will be shared with the Institute of Cancer Research and an group of experts (the Independent Oversight Committee, "IOC" – a HIFU expert, a fetal medicine expert and a statistics expert). The ICR will use this data to check the

performance of the HIFU system after each treatment. The IOC will use this data to check that the balance of negative effects does not outweigh the positive effects from the study and determine if the study is allowed to continue after each participant treated. A copy of your signed consent form will be sent to the Clinical Trials Unit at Cardiff University as they are conducting the qualitative research part of the study and need to have a record of whether consent was given for this part of the study or not by you, the participant. All physical and electronic data shared with Cardiff University will be returned to the sponsor at the end of the study to be archived as described below.

Transparency: details regarding use of data

Imperial College London is the sponsor for this study based in the United Kingdom. We will be using information from you/your twins medical records in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. Imperial College London will keep identifiable information about you and your twins.

- 25 years after the study has finished in relation to data subject consent forms.
- 25 years after the study has completed in relation to primary research data.

Further information on Imperial College London's retention periods may be found at:

https://www.imperial.ac.uk/media/imperial-college/administration-and-support-services/records-and-archives/public/RetentionSchedule.pdf.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you/your twins that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

Imperial College Healthcare NHS Trust will collect information from you and/or your medical records for this research study in accordance with our instructions.

Imperial College Healthcare NHS Trust will use your name, NHS number, hospital number and contact details (email, telephone number, postal address) to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Individuals from Imperial College London and regulatory organisations may look at your medical and research records to check the accuracy of the research study. Imperial College Healthcare NHS Trust will pass these details to Imperial College London along with the information collected from you and/or your medical records. The only people in Imperial College London who will have access to information that identifies you will be people who need to contact you for the research study or to audit the data collection process. The people who analyse the information will not be able to identify you and will not be able to find out your name, NHS number, hospital data or contact details.

Imperial College Healthcare NHS Trust will keep identifiable information about you from this study for25 years after the study has finished.

Your GP and the Consultant Obstetrician overseeing your antenatal care and the hospital where you will receive maternity care will be informed of your involvement in the study.

When you agree to take part in a research study, the information about your health and care may be provided to researchers running other research studies in this organisation and in other organisations. These organisations may be universities, NHS organisations or companies involved in health and care research in this country or abroad. Your information will only be used by organisations and researchers to conduct research in accordance with the UK Policy Framework for Health and Social Care Research**.**

Your information could be used for research in any aspect of health or care, and could be combined with information about you from other sources held by researchers, the NHS or government. Where this information could identify you, the information will be held securely with strict arrangements about who can access the information. The information will only be used for the purpose of health and care research, or to contact you about future opportunities to participate in research. It will not be used to make decisions about future services available to you, such as insurance. Where there is a risk that you can be identified your data will only be used in research that has been independently reviewed by an ethics committee.

You can find out more about how we use your information in this research study by contacting Dr Christoph Lees, Institute of Reproductive and Developmental Biology, Imperial College London, W12 0HS**.**

Legal basis

As universities we use personally-identifiable information to conduct research to improve health, care and services. As a publicly-funded organisation, we have to ensure that it is in the public interest when we use personally-identifiable information from people who have agreed to take part in research. This means that when you agree to take part in a research study, we will use you/your twins data in the ways needed to conduct and analyse the research study.

Health and care research should serve the public interest, which means that we have to demonstrate that our research serves the interests of society as a whole. We do this by following the UK Policy Framework for Health and Social Care Research.

Transfer of your data

When you agree to take part in a research study, the information about you and your twins health and care may be provided to researchers running other research studies in this organisation and in other organisations. These organisations may be universities, NHS organisations or companies involved in health and care research in this country or abroad. You/your twins information will only be used by organisations and researchers to conduct research in accordance with the UK Policy Framework for Health and Social Care Research. This information will not identify you/your twins and will not be combined with other information in a way that could identify you/your twins. The

information will only be used for the purpose of health and care research, and cannot be used to contact you or to affect your care. It will not be used to make decisions about future services available to you, such as insurance.

International transfers

There may be a requirement to transfer information to countries outside the European Economic Area (for example, to a research partner). Where this information contains your personal data, Imperial College London will ensure that it is transferred in accordance with data protection legislation. If the data is transferred to a country which is not subject to a European Commission (EC) adequacy decision in respect of its data protection standards, Imperial College London will enter into a data sharing agreement with the recipient organisation that incorporates EC approved standard contractual clauses that safeguard how you/your twins personal data is processed.

Contact us

If you wish to raise a complaint on how we have handled you/your twins personal data or if you want to find out more about how we use research data, please contact Imperial College London's Data Protection Officer via email at dpo@imperial.ac.uk, via telephone on 020 7594 3502 and via post at Imperial College London, Data Protection Officer, Faculty Building Level 4, London SW7 2AZ.

If you are not satisfied with our response or believe we are processing your personal data in a way that is not lawful you can complain to the Information Commissioner's Office (ICO). The ICO does recommend that you seek to resolve matters with the data controller (us) first before involving the regulator.

In the unlikely event that you lost capacity during this study, you will be withdrawn from the study. Identifiable data or tissue already collected with consent would be retained and used in the study, but no further data or tissue would be collected or any other research procedures carried out.

What if there is a problem?

If you have any concern about any aspect of the study, you should speak with the researcher who will do their best to answer your questions. If for any reason you decide to stop taking part in the study after you have enrolled, then you are able to withdraw your consent. However, if you have been treated with HIFU we may need to see you for one last assessment to check if you need any additional medical care to what you are already receiving.

Imperial College London holds insurance policies which apply to this study. If you experience harm or injury as a result of taking part in this study, you will be eligible to claim compensation without having to prove that Imperial College is at fault. These insurance policies do not include cover for pregnancy, birth defects or fetal injury. This does not affect your legal rights to seek compensation.

If you are harmed due to someone's negligence, then you may have grounds for a legal action. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been treated during the course of this study then you should immediately inform the

Investigator: Dr Christoph Lees. Institute of Reproductive and Developmental Biology, Imperial College London, W12 0HS

The normal National Health Service complaints mechanisms are also available to you. The hospital Patient Advice and Liaison Service (PALS) can give you information on how to do this. Please contact:

PALS Manager
Charing Cross Hospital
Fulham Palace Road
London
W6 8RF
Tel: 020 3313 0088
Imperial.pals@nhs.net

If you are still not satisfied with the response, you may contact the Imperial AHSC Joint Research Compliance Office.

Who is funding the study?

The study has been funded by the Medical Research Council (MRC).

Who has approved the research?

The study has been approved by the London Riverside Research Ethics Committee (20/LO/0029)

For further information please contact:

Chief Investigator:
Professor Christoph Lees
Professor of Obstetrics
Imperial College London
Head of Fetal Medicine and Honorary
Consultant in Obstetrics, Imperial College
Healthcare NHS Trust
Centre for Fetal Care
Queen Charlotte's and Chelsea Hospital
London W12 0HS

Study Manager:
Dr Eleri Owen-Jones
Centre for Trials Research
Neuadd Meirionnydd
Cardiff University
Heath Park
Cardiff CF14 4YS